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BIFURCATION ANALYSIS OF MODEL FOR THE EFFECT OF VACCINATION ON THE TRANSMISSION DYNAMICS OF ROTAVIRUS DISEASE

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Abstract. In this work, we investigated the effect of vaccination on the transmission dynamics of rotavirus disease. Rotavirus can be spread both through direct or indirect transmission contact with infected children or unhygienic environment. Vaccination is administered in three doses. We determined both the disease free equilibrium point, P_0, and the endemic equilibrium point, P^*_{kV}. The disease-free equilibrium point, P_0, is both locally and globally asymptotically stable if the effective reproduction number $R_V < 1$ and unstable if $R_V > 1$. The endemic equilibrium point, P^*_{kV}, for $k = 0, 1, 2, 3$ with vaccination exists if and only if $R_V > 1$. In case of no vaccination, the endemic equilibrium point, P^*_{0V}, has a unique stable endemic equilibrium point whenever the basic reproduction number without vaccination $R_{0V} > 1$ and a backward bifurcation exists. Numerical results show that vaccination reduces the degree of susceptibility and infectiousness when children are exposed to the disease. Hence help to reduce rotavirus disease among children.

1. Introduction

Rotavirus is the most common cause of severe gastroenteritis (diarrhea) in infants and young children (Tate *et al.*, 2012) leading to over 600,000 to 760,000 deaths annually worldwide (Clark *et al.*, 2004; WHO, 2012; Gavi Alliance, 2013). Every infant is expected to be infected with rotavirus within the first years (0-5) of life (CDC, 2009). In the United States rotavirus infections affect approximately 2.7 million children under 5 years of age and result in the hospitalization of 55, 000 children every year (Parashar *et al.*, 1995).

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Each year rotavirus causes an estimated 111 million episodes of diarrhea requiring 2 million hospitalizations and 400,000 deaths in children under 5 years (Kim *et al.*, 2010); 85% of these deaths occurring in low-income countries of Africa (Parashar *et al.*, 2009). In Uganda, every year about 19,700 children under five die due to diarrhea caused by rotavirus (WHO, 2012).

The primary mode of rotavirus transmission is fecal-oral (Hochwald *et al.*, 1999). A confirmed case of rotavirus diarrhea can be defined in a patient with diarrhea containing rotavirus antigen detected by an enzyme immunoassay in a fecal specimen (Tate *et al.*, 2012). Rotavirus can survive for months at room temperature (Romas *et al.*, 1998) and can be passed from one person to another through a set of contaminated hands with the virus or by touching a contaminated surface or object (Butz *et al.*,1993). The virus enters the body through the mouth. Children can spread rotavirus before and after they develop the symptoms (Parashar *et al.*, 1995).

Once infection occurs, the incubation period for rotavirus disease is about 1-3 days (Mastretta *et al.*, 2002; CDC, 2009). Most primary rotavirus infections are associated with acute diarrhea that can lead to dehydration and occasionally to death. Common symptoms involve vomiting and diarrhea for 3-8 days, frequent fever and abdominal pain. Immunity after infection is incomplete but recurrent infections tend to be less severe (Bishop *et al.*, 1973; Parashar *et al.*, 1998). Gastrointestinal symptoms generally resolve in 3-7 days (CDC, 2009).

Many studies about rotavirus immunity have found that maternal antibodies protect younger infants (WHO, 2009) since breast milk contains lactadherine (Morrow *et al.*, 2004) that reduces gastrointestinal infections. Lactadherine is thought to prevent symptomatic rotavirus infection (Newburg *et al.*, 1998) when children are breast fed. Breast milk anti-bodies to rotavirus has however been cited as one of the possible factors for the low rotavirus disease in the low income countries compared to the high income countries (Nelson *et al.*, 1998) but does not kill the virus completely.

Vaccination has proven to be efficacious in preventing rotavirus-related disease, gastrointestinal disease and health-care use in infants and toddlers (Vesikari *et al.,* 2006; Vesikari *et al.*, 2007; Ruiz-Palacios *et al.*, 2006). Two rotavirus vaccines are currently available: Rotarix and Rotateq (WHO, 2009a; CDC, 2013). Both vaccines are torelated, safe,

immunogenic and highly effective (Vesikari *et al.,* 2004). They are administered orally from 2, 4, and 6 months of age (Pan, 2003). Other means like, improving hygiene, sanitation and access to clean water are not sufficiently effective in preventing rotavirus, (Butz *et al.*, 1993).

RotaTeq contains five antigens : G1, G2, G3, G4 and P1 (Kim *et al.,* 2010). It is also a pentavalent bovine-human vaccine (Pan, 2003) that accounts for over 80% of rotavirus related diseases (Vesikari *et al.,* 2004). The RotaTeq vaccine has been proved to have efficacy of approximately 75% against rotavirus gastroenteritis disease, and 100% against severe rotavirus related diseases (Molholland, 2004).

Rotatrix is a single strain of human rotavirus (G1, P[8]) (Pan, 2003) and it was licensed to GlaxoSmithkline (GSK) in Mexico in 2004. It is alive attenuated vaccine administered in 2 doses (WHO, 2009). The development of different rotavirus vaccines has been accepted globally as a number one priority to reduce children mortality as one of the Millennium development goals 2015 (Vesikari *et al.,* 2004).

The WHO has released a global recommendation that all countries include infant rotavirus vaccination in their national immunization programs and the GAVI Alliance has promised to provide financial support for rotavirus vaccination programs to developing countries (Kim *et al.*, 2011; WHO, 2009). Severe dehydrating rotavirus infection occurs primarily among unvaccinated children aged 3-35 months (CDC, 2009). Further studies show that rotavirus vaccines are considered to be the most effective preventation method (Tate *et al.*, 2012).

Various mathematical models for the transmission dynamics have aided our understanding of the important factors driving epidemic patterns of rotavirus diarrhea in the community (Pitzer, 2009; Shim *et al.*, 2001). These models can be used to estimate the expected direct and indirect effects of rotavirus vaccines (Pitzer, 2009; Van *et al*, 2010) and have generated predictions that agree with early observations of the impact of vaccination in the developed countries (Pitzer, 2009).

1.1. **Model Formulation.** In this model, we have both vaccinated and unvaccinated children. The proportion of children that are unvaccinated are denoted by $(1-\rho)$ and these join the susceptible group $S_1(t)$. Recruitment into this compartment is through birth by adults at a rate

Λ. Susceptible children from $S_1(t)$ when exposed, can acquire disease either from the different infected classes $I_j(t)$, $j = 1, 2, 3$ where $I_1(t)$ denotes infected children that are unvaccinated, $I_2(t)$ denotes infected children vaccinated for the first dose, $I_3(t)$ denotes infected children vaccinated for the second dose or from environment class $E(t)$. The force of infection of the unvaccinated children is defined by $\psi(S_1, E, I_j)$, where;

$$\psi(S_1, E, I_j) = \epsilon_1 S_1 \sum_{j=1}^{3} (\theta_j I_j) + \frac{\nu_1 S_1 E}{K + E} \tag{1.1}$$

Basing on (1.1), ϵ_1 measure the degree of susceptibility between S_1 and $I_j(t)$, ν_1 measure the degree of susceptibility between S_1 and $E(t)$, θ_j measures the degree of infectiousness in terms of probability contact with the different infectious classes, $I_j(t)$ and K denotes the level of pathogen concentration in the environment, E(t). Children in the infectious class $I_1(t)$ recover naturally at a rate α_1 while others die due to the disease at a rate d_1.

Furthermore we assume that vaccination is administered in three doses, that is, V_1, denoting children vaccinated for the first dose, V_2, denoting children vaccinated for the second dose and V_3, denoting children vaccinated for the third dose. The proportion of children vaccinated for the first dose is given by ρ. After a period of 4 weeks (CDC, 2009; WHO 2009), children in V_1 either take the second dose or not. A proportion η takes the second dose at a rate τ_1 while $(1 - \eta)$ does not. Those that become susceptible join class $S_2(t)$ at a rate κ_1. These children get exposed to infection at a rate $\psi(S_2, E, I_j)$, where;

$$\psi(S_2, E, I_j) = \epsilon_2 S_2 \sum_{j=1}^{3} (\theta_j I_j) + \frac{\nu_2 S_2 E}{K + E} \tag{1.2}$$

From (1.2), ϵ_2 measure the degree of susceptibility between S_2 and $I_j(t)$, ν_2 measure the degree of susceptibility between S_2 and $E(t)$. Children in $I_2(t)$ die due to disease at a rate d_2, while others recover naturally a rate α_2.

After the second dose, $V_2(t)$, children are vaccinated for the third dose or not. A fraction ϕ is vaccinated for the third dose at a rate τ_2 while $(1 - \phi)$ is not. When the fraction $(1 - \phi)$ is exposed they become susceptible and join the $S_3(t)$ class at a rate κ_2. Children $S_3(t)$ become

infected at a rate $\psi(S_3, E, I_j)$, where;

$$\psi(S_3, E, I_j) = \epsilon_3 S_3 \sum_{j=1}^{3} (\theta_j I_j) + \frac{\nu_3 S_3 E}{K + E} \tag{1.3}$$

Infected children in $I_3(t)$ recover naturally at a rate α_3 while others die due to the disease at a rate d_3.

We further note that the degree of susceptibility and infectiousness vary in different classes. The degree of susceptibility is measured by ϵ_i & ν_i, with $i = 1, 2, 3$ while the degree of infectiousness is measured by $\theta_j, j = 1, 2, 3$. From the model description we take $\theta_1 > \theta_2 > \theta_3$ and $\theta_1 + \theta_2 + \theta_3 = 1$.

Children at $V_3(t)$ lose vaccine immunity at a rate β and they join the susceptible class $S_1(t)$. All recovered children can lose immunity and join the susceptible group $S_1(t)$ at a rate ϵ_4. The pathogen population is generated at a rate γ while Infected children contribute to its enhancement through excretion at rates σ_1, σ_2, and σ_3 from $I_1(t)$, $I_2(t)$ and $I_3(t)$ respectively. The model flow diagram is shown in Figure (1.1). From the above assumptions, descriptions and the model flow chart together lead to the set of non linear- differential equations that describe the dynamics of the disease.

$$\frac{dS_1(t)}{dt} = (1 - \rho)\Lambda - \psi(S_1, E, I_j) + \epsilon_4 R - \mu S_1 + \beta V_3,$$

$$\frac{dV_1(t)}{dt} = \rho\Lambda - (1 - \eta)\kappa_1 V_1 - \eta\tau_1 V_1 - \mu V_1,$$

$$\frac{dS_2(t)}{dt} = (1 - \eta)\kappa_1 V_1 - \psi(S_2, E, I_j) - \mu S_2,$$

$$\frac{dV_2(t)}{dt} = \eta\tau_1 V_1 - (1 - \phi)\kappa_2 V_2 - \phi\tau_2 V_2 - \mu V_2,$$

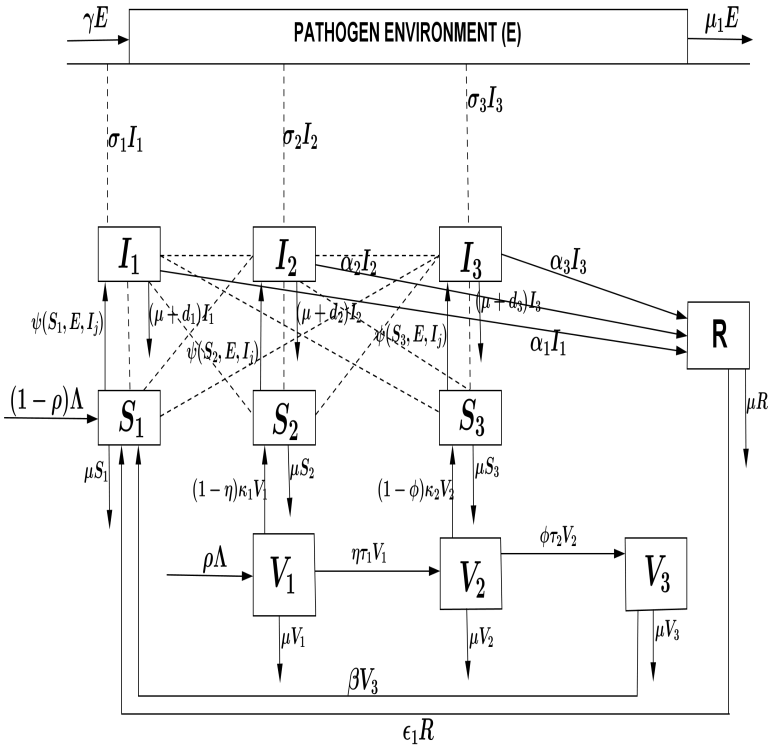

FIGURE 1.1. A schematic of rotavirus disease with both unvaccinated and vaccinated children describing the mechanism of our model

$$
\begin{aligned}
\frac{dV_3(t)}{dt} &= \phi\tau_2 V_2 - \beta V_3 - \mu V_3,\\
\frac{dS_3(t)}{dt} &= (1-\phi)\kappa_2 V_2 - \psi(S_3,E,I_j) - \mu S_3,\\
\frac{dI_1(t)}{dt} &= \psi(S_1,E,I_j) - \alpha_1 I_1 - (\mu+d_1)I_1,\\
\frac{dI_2(t)}{dt} &= \psi(S_2,E,I_j) - \alpha_2 I_2 - (\mu+d_2)I_2,\\
\frac{dI_3(t)}{dt} &= \psi(S_3,E,I_j) - \alpha_3 I_3 - (\mu+d_3)I_3,\\
\frac{dR(t)}{dt} &= \alpha_1 I_1 + \alpha_2 I_2 + \alpha_3 I_3 - \mu R - \epsilon_4 R,\\
\frac{dE(t)}{dt} &= \gamma E - \mu_1 E + \sigma_1 I_1 + \sigma_2 I_2 + \sigma_3 I_3
\end{aligned}
\tag{1.4}
$$

where $\psi(S_1, E, I_i)$, $\psi(S_2, E, I_i)$ and $\psi(S_3, E, I_i)$ are defined in equations (1.1), (1.2) and (1.3) accordingly, with initial conditions:

$S_1(0) = S_{10},\ V_1(0) = V_{10},\ S_2(0) = S_{20},\ V_2(0) = V_{20},\ V_3(0) = V_{30},\ S_3(0) = S_{30},\ I_1(0) = I_{10},$

$I_2(0) = I_{20},\ I_3(0) = I_{30},\ R(0) = R_0\ \ and\ \ N(0) = N_0.$

1.2. **Invariant Region.** Basing on the model (1.4), we assume that all the variables and parameters of the model are positive for all $t \geq 0$. The children population $N(t)$ can be determined by

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - d(I_1 + I_2 + I_3)$$

In absence of rotavirus, there is no death from rotavirus, that is, $d = 0$ then

$$\frac{dN(t)}{dt} \leq \Lambda - \mu N(t) \tag{1.5}$$

Solving for $N(t)$ in (1.5), we get

$$\begin{aligned} N(t) &\leq -\frac{1}{\mu}[(\Lambda - \mu N_0)e^{-\mu t} - \Lambda], \\ \Rightarrow N(t) &\leq \frac{\Lambda}{\mu} - (\frac{\Lambda - \mu N_0}{\mu})e^{-\mu t} \end{aligned} \tag{1.6}$$

For $N_0 < \dfrac{\Lambda}{\mu}$, from (1.6) we have

$$0 \leq N(t) \leq N_0$$

so whatever the case $N(t)$ is bounded above.
That is,

$$N(t) \leq N^* = max\ \{N_0, \frac{\Lambda}{\mu}\} \tag{1.7}$$

This implies that, if there is no disease, that is, $I_j = 0$ for all $j = 1, 2, 3$, $N^* = \dfrac{\Lambda}{\mu}$, is the steady state population which is globally asymptotically stable. Similarly, considering the last differential equation in the system (1.4), that is,

$$\frac{dE(t)}{dt} = \gamma E - \mu_1 E + \sigma_1 I_1 + \sigma_2 I_2 + \sigma_3 I_3,$$

and let the total pathogen population be $E(t)$, then we have

(1.8)
$$\frac{dE(t)}{dt} = (\gamma - \mu_1)E + \sigma_1 I_1 + \sigma_2 I_2 + \sigma_3 I_3 \leq (\gamma - \mu_1)E + (\sigma_1 + \sigma_2 + \sigma_3)N(t),$$
$$\Rightarrow \frac{dE(t)}{dt} \leq (\gamma - \mu_1)E + (\sigma_1 + \sigma_2 + \sigma_3)N(t)$$

But from (1.7), we have $N(t) \leq \frac{\Lambda}{\mu}$, which implies that

(1.9)
$$\frac{dE(t)}{dt} \leq (\gamma-\mu_1)E+(\sigma_1+\sigma_2+\sigma_3)N_C(t) \leq (\gamma-\mu_1)E+(\sigma_1+\sigma_2+\sigma_3)\frac{\Lambda}{\mu}$$

Integrating both sides of (1.9) gives

$$E(t) \leq \frac{(\sigma_1 + \sigma_2 + \sigma_3)\Lambda}{\mu(\mu_1 - \gamma)}[1 + Be^{-(\mu_1-\gamma)t}] \tag{1.10}$$

where B is a constant. The pathogen population size $E(t)$ becomes

$$0 \leq E(t) \leq \frac{(\sigma_1 + \sigma_2 + \sigma_3)\Lambda}{\mu(\mu_1 - \gamma)}$$

provided $\mu_1 > \gamma$.
Therefore, the feasible solution set of the pathogen population of the system (1.4) enters the region

$$\left\{\mathbf{\Omega_C} = (E(t) \in \mathbf{R}_+ | E(t) \leq \frac{(\sigma_1 + \sigma_2 + \sigma_3)\Lambda}{\mu(\mu_1 - \gamma)})\right\}$$

Therefore, the feasible set for our model system (1.4) is given by

$$\begin{aligned} &\left\{\mathbf{\Omega} = (S_1, V_1, S_2, V_2, S_3, V_3, I_1, I_2, I_3, R, E) \in \mathbf{R}_+^{\mathbf{11}} | \right. \\ &(S_1, V_1, S_2, V_2, S_3, V_3, I_1, I_2, I_3, R, E) \geq 0; \\ &\left. N(t) \leq \frac{\Lambda}{\mu}; \;\; E(t) \leq \frac{(\sigma_1 + \sigma_2 + \sigma_3)\Lambda}{\mu(\mu_1 - \gamma)}\right\}. \end{aligned} \tag{1.11}$$

is a positively invariant set under the flow induced by the model system (1.4). Hence the system is biologically meaningful and mathematically well-posed in the domain $\mathbf{\Omega}$.

1.3. **Model Analysis.** We analyze and investigate both existence and stability of the equilibrium points, and the different reproduction numbers.

1.3.1. *Positivity of Solutions.*

Lemma 1. *Let the initial data be*

$\{(S_1(0), V_1(0), S_2(0), V_2(0), S_3(0), V_3(0), I_1(0), I_2(0), I_3(0), R(0), E(0)) \geq 0\} \in \mathbf{R_+^{12}}$.

Then, the solution set

$$\{S_1(t), V_1(t), S_2(t), V_2(t), S_3(t), V_3(t), I_1(t), I_2(t), I_3(t), R(t), E(t)\}$$

of the system (1.4) *is non-negative for all* $t > 0$.

Proof:
From the first equation of the model system (1.4)

$$\frac{dS_1(t)}{dt} = (1-\rho)\Lambda - \psi(S_1, E, I_j) + \epsilon_4 R - \mu S_1 + \beta V_3 \geq -\mu S_1,$$

$$\frac{dS_1(t)}{dt} \geq -\mu S_1.$$

Integrating by separation of variables gives,

$$\int \frac{dS_1(t)}{S_1} \geq \int -\mu dt$$

this gives

$$S_1(t) \geq S_1(0)e^{-\int \mu dt} \geq 0,$$

and using initial conditions $S_1(0) = S_{10}$, gives

$$S_1(t) \geq S_{10}e^{-\mu t} \geq 0, \quad since \quad \mu > 0$$

Considering the second equation of model system (1.4)

$$\frac{dV_1(t)}{dt} = \rho\Lambda - (1-\eta)\kappa_1 V_1 - \eta\tau_1 V_1 - \mu V_1 \geq -((1-\eta)\kappa_1 + \eta\tau_1 + \mu)V_1$$

$$\frac{dV_1(t)}{dt} \geq -((1-\eta)\kappa_1 + \eta\tau_1 + \mu)V_1$$

Integrating on both sides by separation of variables gives,

$$\int \frac{dV_1(t)}{V_1} \geq \int -((1-\eta)\kappa_1 + \eta\tau_1 + \mu)dt$$

this gives

$$V_1(t) \geq V_1(0)e^{-\int((1-\eta)\kappa_1 + \eta\tau_1 + \mu)dt} \geq 0$$

$$since \;\; ((1-\eta)\kappa_1 + \eta\tau_1 + \mu) \geq 0$$

Similarly from the other equations of the system (1.4) we derive the following results:

$$S_2(t) \geq S_2(0)e^{-\int \mu dt} \geq 0, \quad since \quad \mu > 0$$

$$V_2(t) \geq V_2(0)e^{-\int ((1-\phi)\kappa_2+\phi\tau_2+\mu)dt} \geq 0 \quad since \quad ((1-\phi)\kappa_2+\phi\tau_2+\mu) \geq 0$$

$$V_3(t) \geq V_3(0)e^{-\int (\beta+\mu)dt} \geq 0 \quad since \quad (\beta+\mu) \geq 0$$

$$S_3(t) \geq S_3(0)e^{-\int \mu dt} \geq 0, \quad since \quad \mu > 0$$

$$I_1(t) \geq I_1(0)e^{-\int (\alpha_1+\mu+d_1))dt} \geq 0, \quad since \quad (\alpha_1+\mu+d_1)) > 0$$

$$I_2(t) \geq I_2(0)e^{-\int (\alpha_2+\mu+d_2))dt} \geq 0, \quad since \quad (\alpha_2+\mu+d_2)) > 0$$

$$I_3(t) \geq I_3(0)e^{-\int (\alpha_3+\mu+d_3))dt} \geq 0, \quad since \quad (\alpha_3+\mu+d_3)) > 0$$

$$R(t) \geq R(0)e^{-\int (\epsilon_1+\mu)dt} \geq 0 \quad since \quad (\epsilon_4+\mu) \geq 0$$

$$E(t) \geq E(0)e^{\int (\gamma-\mu_1)dt} \geq 0 \quad since \quad (\gamma-\mu_1) \geq 0$$

Hence the components of the solution to system (1.4) are non-negative.

1.3.2. *Disease Free Equilibrium (DFE), P_0.*
Let $P_0 = (S_1^0, V_1^0, S_2^0, V_2^0, S_3^0, I_1^0, I_2^0, I_3^0, R^0, E^0)$ be the disease free equilibrium point. This is obtained by setting the right-hand side of the model system (1.1) to zero. That is,

$$\frac{dS_1(t)}{dt} = \frac{dV_1(t)}{dt} = \frac{dS_2(t)}{dt} = \frac{dV_2(t)}{dt} = \frac{dV_3(t)}{dt} = \frac{dS_3(t)}{dt} = \frac{dR(t)}{dt} = 0$$

This gives

$$\begin{aligned}
0 &= (1-\rho)\Lambda - \psi(S_1, E, I_j) - \mu S_1 + \beta V_3 \\
0 &= \rho\Lambda - ((1-\eta)\kappa_1 + \eta\tau_1 + \mu)V_1, \\
0 &= (1-\eta)\kappa_1 V_1 - \psi(S_2, E, I_j) - \mu S_2, \\
0 &= \eta\tau_1 V_1 - ((1-\phi)\kappa_2 + \phi\tau_2 + \mu)V_2, \\
0 &= (1-\phi)\kappa_2 V_2 - \psi(S_3, E, I_j) - \mu S_3,
\end{aligned} \tag{1.12}$$

with $I_1 = I_2 = I_3 = 0$ & $E = 0$ and therefore, according to (1.1), (1.2) and (1.3), $\psi(S_i, E, I_j) = 0$ for $i, j = 1, 2, 3$.

Solving (1.12), the disease-free equilibrium point, P_0,

$$P_0 = (S_1^0, V_1^0, S_2^0, V_2^0, V_3^0, S_3^0, 0, 0, 0, 0, 0)$$

where

(1.13)

$$S_1^0 = \frac{(1-\rho)\Lambda}{\mu} + \frac{\beta}{\mu}\frac{\phi\tau_2}{(\beta+\mu)}\frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)},$$

$$V_1^0 = \frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)},$$

$$S_2^0 = \frac{(1-\eta)\kappa_1}{\mu}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)},$$

$$V_2^0 = \frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)},$$

$$V_3^0 = \frac{\phi\tau_2}{(\beta+\mu)}\frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)},$$

$$S_3^0 = \frac{(1-\phi)\kappa_2}{\mu}\frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}$$

1.3.3. *The Effective Reproduction Number with Vaccination, R_V.* The effective reproduction number, R_e refers to the average number of new infections generated by a typical infectious individual in a community where intervention strategies are in place. This is computed using the next generation operator approach as described by Van den Driessche and Watmough (2002) as follows.
Let

(i) $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i.
(ii) $\mathcal{V}_i^+(x)$ be the rate of transfer of individuals into compartment i by all other means.
(iii) $\mathcal{V}_i^-(x)$ be the transfer of individuals out of the compartment i.

Then the disease transmission model consists of the system of equations

$$x_i' = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x)$$

where

$$\mathcal{V}_i = \mathcal{V}_i^-(x) - \mathcal{V}_i^+.$$

The next important step is to obtain the disease-free equilibrium point P_0. We then compute matrices F and V which are $m \times m$ matrices, where m represents the infected classes, defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(P_0)\right]$$

and

$$V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(P_0)\right] \quad with \quad 1 \leq i, j \leq m,$$

respectively, F is nonnegative and V is a nonsingular M-matrix (a matrix with inverse, belonging to the class of positive matrices). Thus V^{-1} is nonnegative and consequently FV^{-1} is nonnegative.

We then compute matrix FV^{-1}, defined as the next generation matrix (Diekmann *et al.*, 1990). The effective reproductive number with vaccination R_V is then defined as

$$R_V = \rho(FV^{-1})$$

where $\rho(A)$ is the spectral radius of matrix A (or the maximum modulus of the eigenvalues of A).
Applying the above method. From (1.4), after rearranging our set of equations from the infected class, we derive $\mathcal{F}_i$ and $\mathcal{V}_i$ as

$$\mathcal{F}_i = \begin{bmatrix} \epsilon_1 S_1(\theta_1 I_1 + \theta_2 I_2 + \theta_3 I_3) + \frac{\nu_1 E S_1}{K+E} \\ \epsilon_2 S_2(\theta_1 I_1 + \theta_2 I_2 + \theta_3 I_3) + \frac{\nu_2 E S_2}{K+E} \\ \epsilon_3 S_3(\theta_1 I_1 + \theta_2 I_2 + \theta_3 I_3) + \frac{\nu_3 E S_3}{K+E} \\ 0 \end{bmatrix} \tag{1.14}$$

and

$$\mathcal{V}_i = \begin{bmatrix} (\alpha_1 + \mu + d_1) I_1 \\ (\alpha_2 + \mu + d_2) I_2 \\ (\alpha_3 + \mu + d_3) I_3 \\ (\mu_1 - \gamma) E - \sigma_1 I_1 - \sigma_2 I_2 - \sigma_3 I_3 \end{bmatrix} \tag{1.15}$$

Obtaining the partial derivatives of (1.14) with respect to I_1, I_2, I_3 and E and evaluating at the disease free point P_0 gives

$$F = \begin{bmatrix} \epsilon_1 S_1 \theta_1 & \epsilon_1 S_1 \theta_2 & \epsilon_1 S_1 \theta_3 & \frac{\nu_1 S_1}{K} \\ \epsilon_2 S_2 \theta_1 & \epsilon_2 S_2 \theta_2 & \epsilon_2 S_2 \theta_3 & \frac{\nu_2 S_2}{K} \\ \epsilon_3 S_3 \theta_1 & \epsilon_3 S_3 \theta_2 & \epsilon_3 S_3 \theta_3 & \frac{\nu_3 S_3}{K} \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{1.16}$$

Similarly, the Jacobian matrix of (1.15) works out to be:

(1.17)
$$V = \begin{bmatrix} (\alpha_1+\mu+d_1) & 0 & 0 & 0 \\ 0 & (\alpha_2+\mu+d_2) & 0 & 0 \\ 0 & 0 & (\alpha_3+\mu+d_3) & 0 \\ -\sigma_1 & -\sigma_2 & -\sigma_3 & (\mu_1-\gamma) \end{bmatrix}$$

We then find the inverse of (1.17) which is used to compute FV^{-1} and we have

(1.18)
$$FV^{-1} = \begin{bmatrix} \frac{\epsilon_1 S_1\theta_1}{n_1} + \frac{\nu_1 S_1\sigma_1}{n_1 K(\mu_1-\gamma)} & \frac{\epsilon_1 S_1\theta_2}{n_2} + \frac{\nu_1 S_1\sigma_2}{n_2 K(\mu_1-\gamma)} & \frac{\epsilon_1 S_1\theta_3}{n_3} + \frac{\nu_1 S_1\sigma_3}{n_3 K(\mu_1-\gamma)} & \frac{\nu_1 S_1}{K(\mu_1-\gamma)} \\ \frac{\epsilon_2 S_2\theta_1}{n_1} + \frac{\nu_2 S_2\sigma_1}{n_1 K(\mu_1-\gamma)} & \frac{\epsilon_2 S_2\theta_2}{n_2} + \frac{\nu_2 S_2\sigma_2}{n_2 K(\mu_1-\gamma)} & \frac{\epsilon_2 S_2\theta_3}{n_3} + \frac{\nu_2 S_2\sigma_3}{n_3 K(\mu_1-\gamma)} & \frac{\nu_2 S_2}{K(\mu_1-\gamma)} \\ \frac{\epsilon_3 S_3\theta_1}{n_1} + \frac{\nu_3 S_3\sigma_1}{n_1 K(\mu_1-\gamma)} & \frac{\epsilon_3 S_3\theta_2}{n_2} + \frac{\nu_3 S_3\sigma_2}{n_2 K(\mu_1-\gamma)} & \frac{\epsilon_3 S_3\theta_3}{n_3} + \frac{\nu_3 S_3\sigma_3}{n_3 K(\mu_1-\gamma)} & \frac{\nu_3 S_3}{K(\mu_1-\gamma)} \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

with

$$n_1 = (\alpha_1+\mu+d_1),$$
$$n_2 = (\alpha_2+\mu+d_2),$$
$$n_3 = (\alpha_3+\mu+d_3),$$

at disease free equilibrium $P_0 = (S_1^0, V_1^0, S_2^0, V_2^0, V_3^0, S_3^0, 0, 0, 0, 0, 0)$. The effective reproduction number with vaccination, R_V, is computed as $max_i\{\lambda_i \mid FV^{-1} - \lambda I \mid\} = 0$ for $\lambda_i > 0, i = 1, 2, 3$. Thus, R_V, is given as

(1.19)
$$R_V = \frac{S_1^0}{n_1}\left(\epsilon_1\theta_1 + \frac{\nu_1\sigma_1}{K(\mu_1-\gamma)}\right) + \frac{S_2^0}{n_2}\left(\epsilon_2\theta_2 + \frac{\nu_2\sigma_2}{K(\mu_1-\gamma)}\right) + \frac{S_3^0}{n_3}\left(\epsilon_3\theta_3 + \frac{\nu_3\sigma_3}{K(\mu_1-\gamma)}\right), \ \ \mu_1 > \gamma$$

1.3.4. *Analysis of the Effective Reproduction Number with Vaccination, R_V.* From (1.19), let

$$\Upsilon_1 = \frac{S_1^0}{(\alpha_1+\mu+d)}\left(\epsilon_1\theta_1 + \frac{\nu_1\sigma_1}{K(\mu_1-\gamma)}\right), \ \ \Upsilon_2 = \frac{S_2^0}{(\alpha_2+\mu+d)}\left(\epsilon_2\theta_2 + \frac{\nu_2\sigma_2}{K(\mu_1-\gamma)}\right),$$
$$\Upsilon_3 = \frac{S_3^0}{(\alpha_3+\mu+d)}\left(\epsilon_3\theta_3 + \frac{\nu_3\sigma_3}{K(\mu_1-\gamma)}\right)$$

(a) Considering Υ_1 we have

$$\begin{aligned} \Upsilon_1 &= \frac{S_1^0}{(\alpha_1+\mu+d)}\left(\epsilon_1\theta_1 + \frac{\nu_1\sigma_1}{K(\mu_1-\gamma)}\right) \\ &= \left(\frac{(1-\rho)\Lambda}{\mu(\alpha_1+\mu+d)}\left(\epsilon_1\theta_1 + \frac{\nu_1\sigma_1}{K(\mu_1-\gamma)}\right)\right) + \\ &\quad \left(\frac{\beta}{\mu(\alpha_1+\mu+d)}\frac{\phi\tau_2}{(\beta+\mu)}\frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}\left(\epsilon_1\theta_1 + \frac{\nu_1\sigma_1}{K(\mu_1-\gamma)}\right)\right), \\ &= R_{0V} + R_{3V} \end{aligned}$$

where

$$R_{0V} = \frac{(1-\rho)\Lambda}{\mu(\alpha_1+\mu+d)}\left(\epsilon_1\theta_1 + \frac{\nu_1\sigma_1}{K(\mu_1-\gamma)}\right),$$

$$R_{3V} = \frac{\beta}{\mu(\alpha_1+\mu+d)}\frac{\phi\tau_2}{(\beta+\mu)}\frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}\left(\epsilon_1\theta_1 + \frac{\nu_1\sigma_1}{K(\mu_1-\gamma)}\right)$$

We note that R_{0V} is the basic reproduction number without vaccination and R_{3V} is the effective reproduction for children whose vaccine immunity wanes after the third dose and they become susceptible again.

(b) Considering Υ_2

$$\begin{aligned}\Upsilon_2 &= \frac{S_2^0}{(\alpha_2+\mu+d)}\left(\epsilon_2\theta_2 + \frac{\nu_2\sigma_2}{K(\mu_1-\gamma)}\right),\\ &= \frac{(1-\eta)\kappa_1}{\mu(\alpha_2+\mu+d)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}\left(\epsilon_2\theta_2 + \frac{\nu_2\sigma_2}{K(\mu_1-\gamma)}\right)\\ &= R_{1V}\end{aligned}$$

representing the effective reproduction number of children who receive the first dose of vaccination but they are not taken back for the second dose.

(c) Also considering Υ_3

$$\begin{aligned}\Upsilon_3 &= \frac{S_3^0}{(\alpha_3+\mu+d)}\left(\epsilon_3\theta_3 + \frac{\nu_3\sigma_3}{K(\mu_1-\gamma)}\right)\\ &= \frac{(1-\phi)\kappa_2}{\mu(\alpha_{3+\mu+d})}\frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}\left(\epsilon_3\theta_3 + \frac{\nu_3\sigma_3}{K(\mu_1-\gamma)}\right)\\ &= R_{2V}\end{aligned}$$

We note that Υ_3 denotes the effective reproduction number of children who receive the first dose and second dose but did not go back for the third. We denote Υ_3 by R_{2V}

Thus the effective reproduction with vaccination R_V is given by

$$R_V = R_{0V} + R_{1V} + R_{2V} + R_{3V}$$

in which

(i) R_{0V} is the basic reproduction number without vaccination.
(ii) R_{1V} is the effective reproduction number for children who receive the first dose of vaccination only.

(iii) R_{2V} is the effective reproduction number for children who get first and second doses only.
(iv) R_{3V} is the effective reproduction number for children who receive all doses and when the vaccine waned, they joined the susceptible class again.

1.4. **Local Stability of the Disease-free Equilibrium Point with Vaccination, P_0.** This can be determined by examining the linearised form of the system (1.4) at the disease free state P_0. The Jacobian matrix is computed by differentiating each equation in the system with respect to the state variables. we get
$J_{P_0} =$

(1.20)
$$\begin{bmatrix}
-\mu & 0 & 0 & 0 & \beta & 0 & -\epsilon_1 S_1\theta_1 & -\epsilon_1 S_1\theta_2 & -\epsilon_1 S_1\theta_3 & \epsilon_4 & -\frac{\nu_1 S_1}{K} \\
0 & -\chi_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \chi_6 & -\mu & 0 & 0 & 0 & -\epsilon_2 S_2\theta_1 & -\epsilon_2 S_2\theta_2 & -\epsilon_2 S_2\theta_3 & 0 & -\frac{\nu_2 S_2}{K} \\
0 & \eta\tau_1 & 0 & -\chi_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \phi\tau_2 & -\chi_8 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \chi_7 & 0 & -\mu & -\epsilon_3 S_3\theta_1 & -\epsilon_3 S_3\theta_2 & -\epsilon_3 S_3\theta_3 & 0 & -\frac{\nu_3 S_3}{K} \\
0 & 0 & 0 & 0 & 0 & 0 & \chi_3 & \epsilon_1 S_1\theta_2 & \epsilon_1 S_1\theta_3 & 0 & \frac{\nu_1 S_1}{K} \\
0 & 0 & 0 & 0 & 0 & 0 & \epsilon_2 S_2\theta_1 & \chi_4 & \epsilon_2 S_2\theta_3 & 0 & \frac{\nu_2 S_2}{K} \\
0 & 0 & 0 & 0 & 0 & 0 & \epsilon_3 S_3\theta_1 & \epsilon_3 S_3\theta_2 & \chi_5 & 0 & \frac{\nu_3 S_3}{K} \\
0 & 0 & 0 & 0 & 0 & 0 & \alpha_1 & \alpha_2 & \alpha_3 & -\chi_9 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \sigma_1 & \sigma_2 & \sigma_3 & 0 & (\gamma-\mu_1)
\end{bmatrix}$$

with

$\chi_1 = ((1-\eta)\kappa_1 + \eta\tau_1 + \mu),\ \chi_2 = ((1-\phi)\kappa_2 + \phi\tau_2 + \mu),$

$\chi_3 = \epsilon_1 S_1^0\theta_1 - (\alpha_1 + \mu + d),$

$\chi_4 = \epsilon_2 S_2^0\theta_2 - (\alpha_2 + \mu + d),\ \chi_5 = \epsilon_3 S_3^0\theta_3 - (\alpha_3 + \mu + d), \chi_6 = (1-\eta)\kappa_1,\ \chi_7 = (1-\phi)\kappa_2,$

$\chi_8 = (\beta + \mu), \chi_9 = (\mu + \epsilon_4)$

The local stability of P_0 is determined basing on the signs of the eigenvalues of the Jacobian matrix (1.20). The disease-free equilibrium point, P_0, is said to be locally asymptotically stable if the real parts of the eigenvalues are all negative, otherwise it is said to be unstable. For an eigenvalue λ of matrix (1.20) we have $\mid J_{P_0} - \lambda I \mid = 0$.

Clearly from (1.20), we can easily see that $\lambda_1 = -\mu, \lambda_2 = -((1-\eta)\kappa_1 + \eta\tau_1 + \mu), \lambda_3 = -\mu$
$\lambda_4 = -((1-\phi)\kappa_2 + \phi\tau_2 + \mu), \lambda_5 = -(\beta+\mu), \lambda_6 = -\mu$, and $\lambda_7 = -(\mu+\epsilon_4)$.
The remaining four $\lambda' s$ are evaluated from:

$$det\begin{vmatrix} \chi_3-\lambda & \epsilon_1 S_1\theta_2 & \epsilon_1 S_1\theta_3 & \frac{\nu_1 S_1}{K} \\ \epsilon_2 S_2\theta_1 & \chi_4-\lambda & \epsilon_2 S_2\theta_3 & \frac{\nu_2 S_2}{K} \\ \epsilon_3 S_3\theta_1 & \epsilon_3 S_3\theta_2 & \chi_5-\lambda & \frac{\nu_3 S_3}{K} \\ \sigma_1 & \sigma_2 & \sigma_3 & (\gamma-\mu_1)-\lambda \end{vmatrix} = 0 \tag{1.21}$$

Computing for λ's of matrix (1.21), we get a characteristic equation of a fourth degree as:

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0 \tag{1.22}$$

where

$$\begin{aligned} a_1 &= -\left(\chi_3 + [\chi_4 + (\chi_5 + (\gamma-\mu_1))]\right), \\ a_2 &= \chi_3\left(\chi_4(\chi_5(\gamma-\mu_1) - \sigma_3\frac{\nu_3 S_3}{K})\right) + \\ &\quad \left(\chi_4(\chi_5 + (\gamma-\mu_1)) + (\chi_5(\gamma-\mu_1) - \sigma_3\frac{\nu_3 S_3}{K}) - \epsilon_2 S_2\theta_3\epsilon_3 S_3\theta_2 - \sigma_2\frac{\nu_2 S_2}{K}\right), \\ a_3 &= -\left(\left(\chi_4(\chi_5 + (\gamma-\mu_1)) + (\chi_5(\gamma-\mu_1) - \sigma_3\frac{\nu_3 S_3}{K})\right) - \epsilon_2 S_2\theta_3\epsilon_3 S_3\theta_2 - \sigma_2\frac{\nu_2 S_2}{K}\right)\chi_3 - \\ &\quad \left(\chi_4(\chi_5(\gamma-\mu_1) - \sigma_3\frac{\nu_3 S_3}{K}) + \frac{\nu_2 S_2}{K}(\epsilon_3 S_3\theta_2\sigma_3 - \sigma_2\chi_5) - \epsilon_2 S_2\theta_3((\gamma-\mu_1)\epsilon_3 S_3\theta_2 - \sigma_2\frac{\nu_2 S_2}{K})\right) \\ a_4 &= \left(\chi_4(\chi_5(\gamma-\mu_1) - \sigma_3\frac{\nu_3 S_3}{K}) + (\epsilon_2 S_2\theta_3)(\epsilon_3 S_3\theta_2\sigma_3 - \sigma_2\chi_5) - \epsilon_2 S_2\theta_3((\gamma-\mu_1)\epsilon_3 S_3\theta_2 - \sigma_2\frac{\nu_2 S_2}{K})\right)\chi_3 \end{aligned}$$

Since we have a characteristic equation of degree four, we can analyze this equation by employing the Routh-Hurwitz criteria for stability. Thus from (1.22) for Routh-Hurwitz criteria to hold, the following conditions have to be satisfied.

(i) $a_1 > 0$
(ii) $a_3 > 0$
(iii) $a_4 > 0$
(iv) $a_1a_2a_3 > a_3^2 + a_1^2a_4$

The Routh-Hurwitz criteria is the necessary and sufficient condition for local stability of the system with all the eigenvalues have negative real part. Therefore if we analyze the above itemized conditions we will have,

(i) $a_1 > 0$ if and only if $(\chi_3 + [\chi_4 + (\chi_5 + (\gamma-\mu_1))])$ is negative.
(ii) $a_3 > 0$ if and only if

$$\left(\left(\chi_4(\chi_5 + (\gamma-\mu_1)) + (\chi_5(\gamma-\mu_1) - \sigma_3\frac{\nu_3 S_3}{K})\right) - \epsilon_2 S_2\theta_3\epsilon_3 S_3\theta_2 - \sigma_2\frac{\nu_2 S_2}{K}\right)\chi_3 - \left(\chi_4(\chi_5(\gamma-\mu_1) - \sigma_3\frac{\nu_3 S_3}{K}) + \frac{\nu_2 S_2}{K}(\epsilon_3 S_3\theta_2\sigma_3 - \sigma_2\chi_5) - \epsilon_2 S_2\theta_3((\gamma-\mu_1)\epsilon_3 S_3\theta_2 - \sigma_2\frac{\nu_2 S_2}{K})\right)$$

it is negative.

(iii) $a_4 > 0$ if and only if

$$\left(\chi_4(\chi_5(\gamma-\mu_1)-\sigma_3\frac{\nu_3 S_3}{K})+(\epsilon_2 S_2\theta_3)(\epsilon_3 S_3\theta_2\sigma_3-\sigma_2\chi_5)\chi_3\right) > \left(\epsilon_2 S_2\theta_3((\gamma-\mu_1)\epsilon_3 S_3\theta_2-\sigma_2\frac{\nu_2 S_2}{K})\right)\chi_3$$

(iv) Since the above three critical conditions hold, after algebraic computations it can be shown that $a_1a_2a_3 > a_3^2 + a_1^2a_4$ holds.

Since the first seven eigenvalues of matrix (1.20) are negative and also matrix (1.21) obeys the Routh-Hurwitz conditions shown above, thus the following theorem holds.

Theorem 1.1. *The disease-free equilibrium point P_0 of model system (1.4) is locally asymptotically stable if $R_V < 1$ and unstable if $R_V > 1$.*

1.5. **The Global Stability of Disease Free Equilibrium Point with Vaccination (DFE), P_0.** To determine the global stability of disease free equilibrium point with vaccination, P_0, we use the comparison approach by (Diekmann *et al.,* 1990), we consider the variables representing the infected components and their rates of change of these variables. It follows that at disease free equilibrium point, P_0, $I_1 = I_2 = I_3 = 0$, thus

$$\begin{bmatrix} \frac{dI_1(t)}{dt} \\ \frac{dI_2(t)}{dt} \\ \frac{dI_3(t)}{dt} \\ \frac{dE(t)}{dt} \end{bmatrix} = (F-V)\begin{bmatrix} I_1(t) \\ I_2(t) \\ I_3(t) \\ E(t) \end{bmatrix} - \begin{bmatrix} \nu_1 E\left(\frac{S_1}{K}-\frac{S_1^0}{K+E}\right) \\ \nu_2 E\left(\frac{(1-\eta)\kappa_1}{\mu}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)K}-\frac{S_2^0}{K+E}\right) \\ \nu_3 E\left(\frac{(1-\phi)\kappa_2}{\mu K}\frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+eta\tau_1+\mu)}-\frac{S_3^0}{K+E}\right) \\ 0 \end{bmatrix}$$

where the matrices F and V are defined in equations (1.16) and (1.17) respectively.

At disease free equilibrium point we have:

$\frac{S_1^0}{K+E} \leq \frac{(1-\rho)\Lambda}{\mu} + \frac{\beta}{\mu}\frac{\phi\tau_2}{(\beta+\mu)}\frac{\eta\tau_1}{((1-\phi)\tau_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}$ for all $t \geq 0$.

Similarly, $\frac{S_2^0}{K+E} \leq \frac{(1-\eta)\kappa_1}{\mu}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}$, and,

$\frac{S_3^0}{K+E} \leq \frac{(1-\phi)\kappa_2}{\mu}\frac{\eta\tau_1}{((1-\phi)\kappa_2+\phi\tau_2+\mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}$ for all $t \geq 0$.

Thus it can be seen that

$$\begin{bmatrix} \frac{dI_1(t)}{dt} \\ \frac{dI_2(t)}{dt} \\ \frac{dI_3(t)}{dt} \\ \frac{dE(t)}{dt} \end{bmatrix} \leq (F-V)\begin{bmatrix} I_1(t) \\ I_2(t) \\ I_3(t) \\ E(t) \end{bmatrix} \tag{1.23}$$

Since all the eigenvalues of the matrix $(F - V)$ have negative real parts, it implies that (1.23) is stable if $R_{0V} < 1$ and as $t \longrightarrow \infty$, we will have $I_1 \longrightarrow 0$, $I_2 \longrightarrow 0$, $I_3 \longrightarrow 0$, and $E \longrightarrow 0$. Therefore by comparison theorem in Lakshmikantham *et al.* (1989), it follows that $(I_1, I_2, I_3, E) \longrightarrow (0, 0, 0, 0)$ and the three remaining equations of model system (1.1) gives us solutions as in (1.13).
Thus $(S_1, V_1, S_2, V_2, V_3, S_3, I_1, I_2, I_3, R, E) \longrightarrow P_0$ as $t \longrightarrow \infty$ for $R_{0V} < 1$, implying that P_0 is globally asymptotically stable. Hence the following theorem holds.

Theorem 1.2. *If $R_V < 1$, the disease free equilibrium point, P_0, of the model system* (1.4) *is globally asymptotically stable and unstable if $R_V > 1$.*

1.6. **The Endemic Equilibrium Point (EEP) with Vaccination, P^*_{kV}.** The endemic equilibrium point with vaccination, P^*_{kV}, $k = 0,\ 1,\ 2,\ 3$, where P^*_{0V} represents the EEP without vaccination, P^*_{1V}, with first dose of vaccination, P^*_{2V}, second dose of vaccination and P^*_{3V}, third dose of vaccination, is obtained by setting the model system (1.4) to zero. This is done by expressing all our state variables in terms of the force of infection, that is,

$$\psi^*(S^*_i, E^*, I^*_j) = \left(\epsilon_i S^*_i \sum_j^3 (\theta_j I^*_j) + \frac{\nu_i S^*_i E^*}{K + E^*}\right),\ i, j = 1, 2, 3. \tag{1.24}$$

After algebraic computations, we get the following expressions:

(1.25)

$$\begin{aligned}
S^*_1 &= \frac{1}{\mu}\left[(1-\rho)\Lambda - \psi^*_1 + \epsilon_4 R^* + \beta V^*_3\right],\\
V^*_1 &= \frac{\rho\Lambda}{((1-\eta)\kappa_1 + \eta\tau_1 + \mu)}, \quad S^*_2 = \frac{(1-\eta)\kappa_1}{\mu} V^*_1,\\
V^*_2 &= \frac{\eta\tau_1}{((1-\phi)\kappa_2 + \phi\tau_2 + \mu)} V^*_1, \quad V^*_3 = \frac{\phi\tau_2}{(\beta+\mu)} V^*_2 V^*_1,\\
S^*_3 &= \frac{(1-\phi)\kappa_2}{\mu} V^*_2 - \frac{\psi^*_3}{\mu},\\
I^*_1 &= \frac{\psi^*_1}{(\alpha_1 + \mu + d_1)}, \quad I^*_2 = \frac{\psi^*_2}{(\alpha_2 + \mu + d_2)}, \quad I^*_3 = \frac{\psi^*_3}{(\alpha_3 + \mu + d_3)},\\
R^* &= \frac{\alpha_1 I^*_1 + \alpha_2 I^*_2 + \alpha_3 I^*_3}{(\mu + \epsilon_4)}, \quad E^* = \frac{(\sigma_1 I^*_1 + \sigma_2 I^*_2 + \sigma_3 I^*_3)}{(\mu_1 - \gamma)}.
\end{aligned}$$

To establish the existence and stability of the endemic equilibrium point with vaccination, P^*_{kV}, for $k = 0,\ 1,\ 2,\ 3$, of (1.4), we will examine four cases:

(i) without vaccination, P^*_{0V}
(ii) with first dose of vaccination, P^*_{1V}
(iii) with second dose of vaccination, P^*_{2V}
(iv) with third dose of vaccination, P^*_{3V}

1.6.1. *Case one: Endemic Equilibrium Point without Vaccination, P^*_{0V}.* The endemic equilibrium point without vaccination, P^*_{0V}, is obtained when $\psi^*_2 = \psi^*_3 = 0$. Thus (1.24) reduces to

$$\psi^*_1 = \epsilon_1 S^*_1(\theta_1 I^*_1) + \frac{\nu_1 S^*_1 E^*}{K + E^*} \tag{1.26}$$

where

$$S^*_1 = \frac{1}{\mu}(\Lambda - \psi^*_1(1 - \mathbf{M})), \quad \mathbf{M} = \frac{\epsilon_4}{(\mu+\epsilon_4)}\frac{\alpha_1}{(\alpha_1+\mu+d)}, \quad I^*_1 = \frac{\psi^*_1}{(\alpha_1+\mu+d)}, \quad E^* = \frac{\sigma_1 I^*_1}{(\mu_1-\gamma)}$$

Substituting $S^*_1,\ I^*_1,\ E^*$ into (1.26) we get the following equation in terms of ψ^*_1.

$$\psi^*_1 f(\psi^*_1) = \psi^*_1(A\psi^{*2}_1 + B\psi^*_1 + C) = 0 \tag{1.27}$$

where

$$A = \left(\frac{\sigma_1}{(\mu_1-\gamma)(\alpha_1+\mu+d)}\right)\left(\frac{\epsilon_4}{(\mu+\epsilon_4)}\frac{\alpha_1}{(\alpha_1+\mu+d)}\right)\vartheta_1.$$

$$B = \vartheta_1\left(\frac{K\epsilon_4\alpha_1}{(\mu+\epsilon_4)(\alpha_1+\mu+d)} + \frac{\sigma_1\Lambda}{(\mu_1-\gamma)(\alpha_1+\mu+d)} - K\right) + \vartheta_2\left(\frac{\epsilon_4\alpha_1}{(\mu+\epsilon_4)(\alpha_1+\mu+d)} - 1\right) - \vartheta_3\left(1 - \frac{\epsilon_1\theta_1}{\mu(\alpha_1+\mu+d)}\right)$$

$$C = \frac{K\Lambda\epsilon_1\theta_1}{\mu(\alpha_1+\mu+d)} + \frac{\nu_1\sigma_1\Lambda}{\mu(\mu_1-\gamma)(\alpha_1+\mu+d)} - K$$

$$\vartheta_1 = \left(\frac{\epsilon_1}{\mu}\frac{\theta_1}{(\alpha_1+\mu+d)}\right), \quad \vartheta_2 = \left(\frac{\nu_1\sigma_1}{\mu(\mu_1-\gamma)(\alpha_1+\mu+d)}\right), \quad \vartheta_3 = \left(\frac{\sigma_1}{(\mu_1-\gamma)(\alpha_1+\mu+d)}\right)$$

C can be reduced further to $R_{0V} - 1$ as follows:

$$\begin{aligned} C &= \frac{\Lambda}{\mu(\alpha_1+\mu+d)}\left(\epsilon_1\theta_1 + \frac{\nu_1\sigma_1}{K(\mu_1-\gamma)}\right) - 1 \\ &= R_{0V} - 1 \end{aligned}$$

From (1.27), the endemic equilibrium point without vaccination, P^*_{0V} has three roots, that is, when $\psi^*_1 = 0$ giving the first root which corresponds to the disease free equilibrium point (DFE) and $A\psi^{*2}_1 + B\psi^*_1 +$

$C = 0$ which has the remaining two roots corresponding to the endemic equilibrium point (EEP). These two roots are presented graphically as shown in Figure 1.2 and Figure 1.3. In Figure 1.2, we present the nature

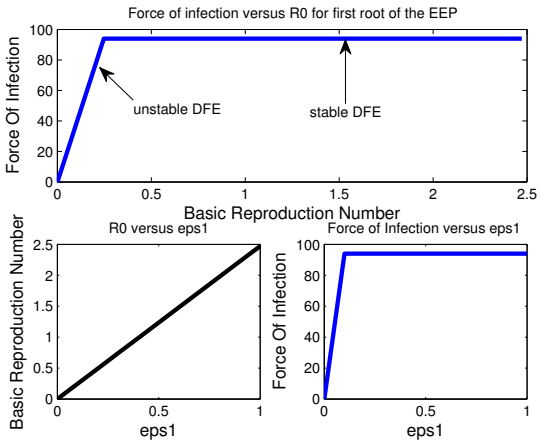

FIGURE 1.2. When we plot force of infection (FOI) versus basic reproduction number, R_{0V} (top plot), we note that as FOI increases also R_{0V} increases, but when $R_0 = 0.25$ the FOI becomes constant thus we except no more spread of the disease. It will only keep in an endemic steady state. Again, when we vary R_{0V} versus direct contact transmission rate (ϵ_1), these are directly proportional to each other. Finally, we note that when we plot FOI versus ϵ_1 still FOI increases and when $\epsilon_1 = 0.25$, the disease goes into an endemic steady state.

of the first root to have a unique equilibrium point with no backward bifurcation while in Figure 1.3, we present the nature of the second root which has both the stable disease free equilibrium (DFE) region and unstable endemic equilibrium point (EEP) region. We further note that Figure 1.3 has a backward bifurcation that occurs when the basic reproduction number without vaccination, $R_{0V} = 1$. This is clearly seen when we plot force of infection (FOI) versus (R_{0V}). Therefore after the analysis of the two endemic equilibrium roots without vaccination the following theorem holds.

Theorem 1.3. *The endemic equilibrium point without vaccination, P^*_{0V}, has a unique stable endemic equilibrium point if and only if $R_{0V} > 1$*

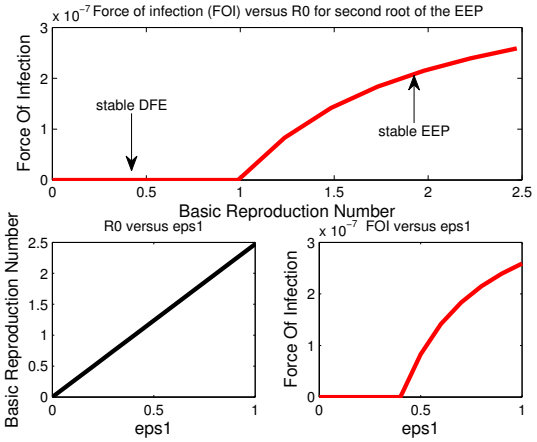

FIGURE 1.3. When we plot force of infection (FOI) against R_0 in the top plot, we note a stable disease free region when FOI= 0 and when $R_0 = 1$, the FOI starts to increase in the stable endemic region where we note that the disease starts to spread again hence a backward bifurcation. When R_0 versus direct transmission contact rate (ϵ_1), these are directly proportional and when we plot FOI versus eps1, we still experience a backward bifurcation when $\epsilon_1 = 0.4$.

1.6.2. *Case two: Endemic Equilibrium Point with First Dose of Vaccination, P^*_{1V}.* The endemic equilibrium point with first dose of vaccination, P^*_{1V}, will be obtained when $\psi^*_1 = \psi^*_3 = 0$. This is because ψ^*_1 is the force of transmission without vaccination. And ψ^*_3 is the force of transmission under second dose of vaccination.
Thus (1.24) is reduced to

$$\psi^*_2 = \epsilon_2 S^*_2(\theta_2 I^*_2) + \frac{\nu_2 S^*_2 E^*}{K + E^*} \tag{1.28}$$

substituting the expressions for S^*_2, I^*_2, and E^* from (1.28), the endemic equilibrium satisfy the following equation

$$\psi^*_2 f(\psi^*_2) = \psi^*_2(A\psi^{*2}_2 + B\psi^*_2 + C) = 0 \tag{1.29}$$

where

$$A = \epsilon_2\theta_2\sigma_2$$
$$B = \mu n_2\sigma_2 - (\mu\epsilon_2\sigma_2 S_2^*\sigma_2 - \epsilon_2\theta_2 K n_2(\mu_1-\gamma) - \mu n_2\nu_2\sigma_2)$$
$$S_2^* = \frac{(1-\eta)\kappa_1}{\mu}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}$$
$$C = \mu n_2 K n_2(\mu_1-\gamma) - (\mu\epsilon_2\theta_2 S_2^* K n_2(\mu_1-\gamma) + \mu n_2\nu_2 S_2^*\sigma_2)$$

C can be reduced further to $1 - R_{1V}$ as follows:

$$\begin{aligned} C &= 1 - \left(\frac{\epsilon_2\theta_2 S_2^*}{n_2} + \frac{\nu_2\sigma_2 S_2^*}{K n_2(\mu_1-\gamma)}\right) \\ &= 1 - \frac{S_2^*}{n_2}\left(\epsilon_2\theta_2 + \frac{\nu_2\sigma_2}{K(\mu_1-\gamma)}\right) \\ &= 1 - \frac{(1-\eta)\kappa_1}{(\alpha_2+\mu+d)\mu}\frac{\rho\Lambda}{((1-\eta)\kappa_1+\eta\tau_1+\mu)}\left(\epsilon_2\theta_2 + \frac{\nu_2\sigma_2}{K(\mu_1-\gamma)}\right) \\ &= 1 - R_{1V} \end{aligned}$$

Solutions of (1.29) are $\psi_2^* = 0$ and $f(\psi_2^*) = 0$. $\psi_2^* = 0$ corresponds to disease free equilibrium point (DFE) whose stability has been established under Section 1.3 and $f(\psi_2^*) = 0$ corresponds to a situation when the disease persists (endemic). In case of backward bifurcation, multiple endemic equilibrium must exist. This implies that equation (1.29) indicates that there are three cases we have to consider of $f(\psi_2^*) = 0$ depending on the signs of B and C since A is always positive. That is,

(1) If $B < 0$ and $C = 0$ or $B^2 - 4AC = 0$, then equation (1.29) has a unique endemic equilibrium point (one positive root) and no backward bifurcation possibility.
(2) If $C > 0$, $B > 0$ and $B^2 - 4AC > 0$, then equation (1.29) has two endemic equilibria (two positive roots), and therefore it's possible for backward bifurcation to occur.

However it's important to note that C is always positive if $R_{1V} < 1$ and negative if $R_{1V} > 1$.

Theorem 1.4. *The rotavirus model with first dose of vaccination has,*

(i) *Precisely one unique endemic equilibrium if* $C < 0 \iff R_{1V} > 1$
(ii) *Precisely two endemic equilibrium if* $C > 0$, $B < 0$ *and* $B^2 - 4AC > 0$
(iii) *None otherwise*

By this result, Theorem 1.4 gives a condition for existence of endemic equilibrium point with first dose of vaccination.

Theorem 1.5. *The endemic equilibrium P^*_{1V}, with first dose of vaccination exists if and only if $R_{1V} > 1$*

1.6.3. *Case three: Endemic Equilibrium Point with Second Dose of Vaccination, P^*_{2V}.* The endemic equilibrium point with second dose of vaccination, P^*_{2V} will be obtained when $\psi^*_1 = \psi^*_2 = 0$. This is because ψ^*_1 is the force of transmission without treatment and vaccination. And ψ^*_2 is the force of transmission under treatment and first dose of vaccination.
Again (1.24) reduces to:

$$\psi^*_3 = \epsilon_3 S^*_3(\theta_3 I^*_3) + \frac{\nu_3 S^*_3 E^*}{K + E^*} \tag{1.30}$$

substituting the expressions for S^*_3, I^*_3, and E^* from (1.30), the endemic equilibrium satisfy the following equation

$$\psi^*_3 f(\psi^*_3) = \psi^*_3(A\psi^{*2}_3 + B\psi^*_3 + C) = 0 \tag{1.31}$$

where

$$\begin{aligned}
A &= \epsilon_3\theta_3\sigma_3 \\
B &= \mu n_3\sigma_3 - (\mu\epsilon_3\sigma_3 S^*_3\sigma_3 - \epsilon_3\theta_3 K n_3(\mu_1 - \gamma) - \mu n_3\nu_3\sigma_3) \\
S^*_3 &= \frac{(1-\phi)\kappa_2}{\mu}\frac{\eta\tau_1}{((1-\phi)\kappa_2 + \phi\tau_2 + \mu)}\frac{\rho\Lambda}{((1-\eta)\kappa_1 + \eta\tau_1 + \mu)} \\
C &= \mu n_3 K n_3(\mu_1 - \gamma) - (\mu\epsilon_3\theta_3 S^*_3 K n_3(\mu_1 - \gamma) + \mu n_3\nu_2 S^*_3\sigma_3)
\end{aligned}$$

C can be reduced further to $1 - R_{2V}$ as follows:

$$\begin{aligned}
C &= 1 - \left(\frac{\epsilon_3\theta_3 S^*_3}{n_3} + \frac{\nu_3\sigma_3 S^*_3}{K n_3(\mu_1 - \gamma)}\right) \\
&= 1 - \frac{S^*_3}{n_3}\left(\epsilon_3\theta_3 + \frac{\nu_3\sigma_3}{K(\mu_1 - \gamma)}\right) \\
&= 1 - R_{2V}
\end{aligned}$$

Applying the same procedure used in analyzing equations (1.29) to (1.31), we note that C is always positive if $R_{2V} < 1$ and negative if $R_{2V} > 1$ leading to Theorem 1.6.

Theorem 1.6. *The rotavirus model with second dose of vaccination has,*

(i) *Precisely one unique endemic equilibrium if $C < 0 \iff R_{2V} > 1$*
(ii) *Precisely two endemic equilibrium if $C > 0$, $B < 0$ and $B^2 - 4AC > 0$*
(iii) *None otherwise*

Depending on this result, Theorem 1.6 gives a condition for existence of endemic equilibrium point with second dose of vaccination.

Theorem 1.7. *The endemic equilibrium P^*_{2V}, with second dose of vaccination exists if and only if $R_{2V} > 1$*

1.6.4. *Case four: Endemic Equilibrium Point with third dose of Vaccination, P^*_{3V}.* Having looked at the three cases above, in a similar way we can still verify the endemic equilibrium point for third dose of vaccination, R_{3V}. Since the four reproduction numbers, that is, R_{0V}, R_{1V}, R_{2V} and R_{3V} come from R_V which we have already considered. Thus

Theorem 1.8. *The endemic equilibrium P^*_{kV}, with vaccination exists if and only if $R_V > 1$.*

2. Numerical Simulations

From our model (1.4) we verified some of the analytical results numerically . This was done using a set of parameters whose sources are mainly from Literature as well as assumptions. Some of the data was obtained from Uganda National private hospitals where rotavirus vaccines are mostly given. We divided the model into four subsections, that is,

(i) without vaccination (S_1I_1RE),
(ii) with first dose of vaccination ($V_1S_2I_2RE$),
(iii) with second dose of vaccination ($V_2S_3I_3RE$),
(iv) we assume no or minimal infection after the third dose of vaccination,

such that we reduce the complexity of the model during simulation. We simulated the model using Matlab ODE solvers. However we only simulated (i) and (ii) since the results in (iii) showed minimal change from those in (ii). The numerical simulations of model (1.4) was carried out using the set of parameter values given in Table 2.1.

2.1. **Without vaccination** (S_1I_1RE)**.** We assumed our initial conditions as $S_1(0) = 1000, I_1(0) = 100, R(0) = 0, E(0) = 100$. We investigated the effect of both direct and indirect contact rates on the transmission dynamics of rotavirus disease. Considering direct transmission we varied different rates of ϵ_1 while for indirect transmission we varied ν_1. We further investigated the effect of shedding rate of infected children on the environment.

Table 2.1 : Parameters values of the Model system (1.4)

Parameter	Description	Value	Source
Λ	birth rate	$0.0018day^{-1}$	[35]
ρ	proportion of unvaccinated	0.5	Estimated
ϵ_1	degree of susceptibility between S_1 & I_i	$0.00052day^{-1}$	Estimated
μ	death rate	$0.0018day^{-1}$	[35]
ϵ_2	degree of susceptibility between S_2 & I_i	$0.00042day^{-1}$	[5]
ϵ_3	degree of susceptibility between S_3 & I_i	$0.00032day^{-1}$	[5,16]
ν_1	degree of susceptibility between S_1 & E	$0.002day^{-1}$	[5,7]
ν_2	degree of susceptibility between S_2 & E	$0.001day^{-1}$	[5,14]
ν_3	degree of susceptibility between S_3 & E	$0.0015day^{-1}$	[8,9]
θ_1	degree of infectiousness between S_1 & I_i	0.5	Assumed
θ_2	degree of infectiousness between S_2 & I_i	0.3	Assumed
θ_3	degree of infectiousness between S_3 & I_i	0.2	Assumed
ϵ_4	natural immunity warning rate	$0.0027day^{-1}$	[6]
β	vaccine warning rate	$0.00274day^{-1}$	[13, 14]
ρ	rate of vaccination for dose one	$0.060179day^{-1}$	Estimated
τ_1	rate of vaccination for dose two	$0.0357day^{-1}$	Estimated
τ_2	rate of vaccination for dose three	0.0157	Estimated
κ_1	rate of not receiving dose two	0.5	Assumed
κ_2	rate of not receiving dose three	0.2	Assumed
α_1	recovery rate from I_1	$0.2day^{-1}$	[11,18]
α_2	recovery rate from I_2	$0.33day^{-1}$	[11,18,32]
α_3	recovery rate from I_3	$0.667day^{-1}$	[11,18]
d_1	death rate without vaccination	$0.0004466day^{-1}$	[30]
d_2	death rate with first dose	$0.00004466day^{-1}$	Assumed
d_3	death rate with second dose	$0.000004466day^{-1}$	Assumed
σ_1	shedding rate of I_1	$10 - 100cellsL^{-1}$	[1, 7]
σ_2	shedding rate of I_2	$5 - 100cellsL^{-1}$	[28,30]
σ_3	shedding rate of I_3	$0 - 100cellsL^{-1}$	[1,8]
μ_1	free-pathogen death rate	$0.0667day^{-1}$	[6]

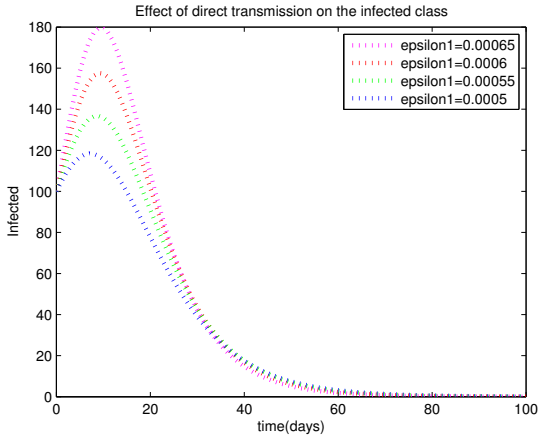

FIGURE 2.1. Effect of direct transmission (ϵ_1) on the infected class

2.1.1. *Effect of direct transmission* (ϵ_1) *on the infected class.* In Figure 2.1 we note that an increase in the rate of direct contact rate (ϵ_1)

between susceptible children and infected ones, increases the number of infected children with rotavirus disease. Thus we should ensure that the level of contact of infected children is reduced as much as possible to lower disease transmission.

2.1.2. *Effect of indirect transmission* (ν_1) *on the infected class.* In Figure 2.2 it is noted that as we reduce the rate of indirect contact (ν_1) between susceptible children and exposed environment, the number of infected children reduces while in case of high contact rate, (ν_1), the number of infected children increases. Thus we should fight to make our environments as clean as we can such that children do not contract the disease from dirty environments. This can be achieved by practicing proper hygiene and sanitation.

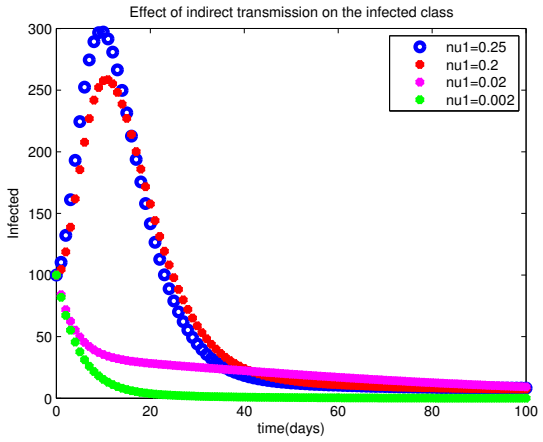

FIGURE 2.2. Effect of indirect transmission (ν_1) on the infected class

2.1.3. *Effect of the shedding rate* (σ_1) *on the environment class.* In Figure 2.3 when the rate at which infected children shed off (σ_1) to the environment is low, there is less pathogens shed off to the environment and so less infection will be caused compared to when there is high shedding rate (σ_1) of infected child to the environment.

2.2. **With first dose vaccination** ($V_1S_2I_2RE$)**.** Under this Section, we want to understand the effect of vaccination on the susceptible, infected and the environment classes. Here, we vary the rate at which children vaccinated for the first dose (κ_1) join these class. We assume that in case children are vaccinated, we expect many children to become less susceptible, few children in the infected class and low shedding rate to the environment class.

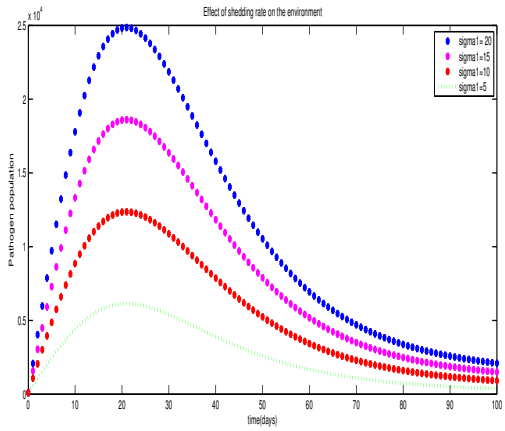

FIGURE 2.3. Effect of the shedding rate (σ_1) on the environment class

2.2.1. *Effect of vaccination on the susceptible class.* In Figure 2.4 when the rate at which, children vaccinated for the first dose leave the vaccinated class to the susceptible class is little or small, very few children will move to the infected class and in case it is high, many are going to be exposed to the disease whom in the long run will become infected and join the infected class. Thus we should ensure to keep the rate (κ_1) as low as we can to reduce the degree of susceptibility to disease.

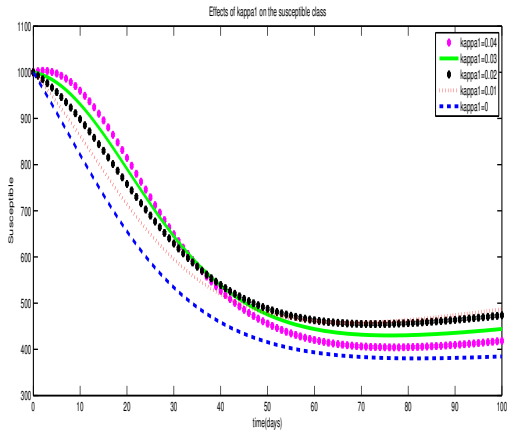

FIGURE 2.4. Effect of κ_1 on the susceptible class

2.2.2. *Effect of vaccination on the infected class.* In Figure 2.5 if the rate at which vaccinated children move to the infected class is high, many children are going to become infected but if the rate is very low,

less children are going to be infected. This implies that, in case (κ_1) is maintained as low as possible, the degree of infectiousness will be low and vice versa.

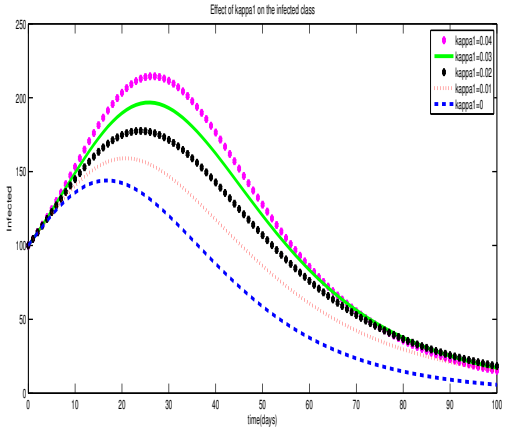

FIGURE 2.5. Effect of κ_1 on the infected class

2.2.3. *Effect of vaccination on the environment class.* In Figure 2.6 it is noted that if the rate at which children vaccinated for the first dose and joining the susceptible class S_2 is very high, we expect many to become exposed to the disease who will later become infected. Due to infection, there will be high growth rate of pathogens in the environment compared to when κ_1 is very low.

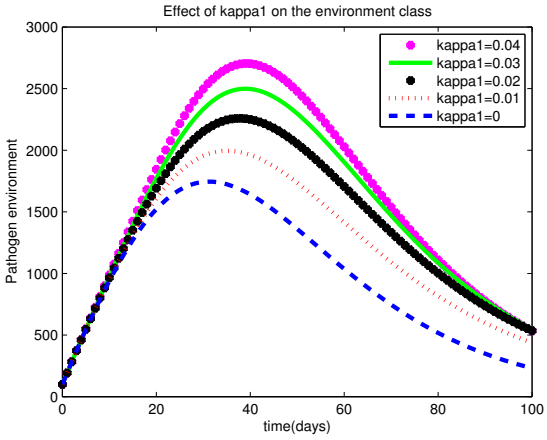

FIGURE 2.6. Effect of κ_1 on the environment class

2.3. **Conclusions.** This study formulated a mathematical model for the transmission dynamics of rotavirus disease. We included three different doses being administered as the case of Uganda. Both the disease free equilibrium (DFE) and endemic equilbrium points (EEP) were determined. Applying the Routh-Hurwitz criteria, the disease-free equilibrium point, P_0, is locally asymptotically stable if, the effective reproduction number with vaccination (R_V), $R_V < 1$ and unstable if $R_V > 1$. The endemic equilibrium point, P^*_{kV}, with vaccination exists if and only if $R_V > 1$. Further more, in case of no vaccination, the endemic equilibrium point without vaccination, P^*_{0V}, has a unique stable endemic equilibrium point if and only if the basic reproduction number without vaccination, $R_{0V} > 1$ and a backward bifurcation exists as shown in Figure 1.3 when $R_{0V} = 1$. Our numerical results show that both direct and indirect transmission contact rates play a high role in the transmission of rotavirus disease. Since vaccination helps to reduce the number of infected children thus it should be used to fight rotavirus among children. Again the environment should also be thoroughly cleaned to reduce the effect of children to environment transmission.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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